Complement in the immunopathogenesis of rheumatic disease

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Abstract | The complement system has vital protective functions as a humoral component of the innate immune system and also through interactions with the adaptive immune system; however, when inappropriately activated or regulated, complement can cause inflammation and organ damage, and such processes are involved in the pathogenesis of many inflammatory conditions, not least rheumatic diseases. Furthermore, states of complement deficiency can predispose not only to infections, but also to autoimmune disorders, including rheumatic diseases such as systemic lupus erythematosus. In this Review, the mechanisms behind the pathogenic activities of complement in rheumatic diseases are discussed. Potential approaches to therapeutic intervention that focus on regulating complement activities in these disorders are also considered.

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Introduction

The complement system is phylogenetically old, and represents an essential part of the innate immune system. Complement comprises more than 30 proteins, which through a complex network of interactions bestow the capacity to defend against invasion by microbes, clear waste products (e.g. immune complexes [ICs], apoptotic material) and regulate cytokine production by immune cells, thus providing an interface between the innate and the adaptive immune systems.

The importance of complement to host protection is highlighted by the susceptibility of individuals deficient in various components of this system to recurrent infectious diseases. Moreover, deficiencies in a number of complement proteins and/or aberrant activity of the complement system are increasingly recognized as contributors to the pathogenetic immune responses that underlie the development and progression of various inflammatory and autoimmune disorders, including rheumatic diseases such as systemic lupus erythematosus (SLE). This Review describes the current understanding of complement system involvement in not only the pathogenesis of rheumatological conditions, but also protection against a spectrum of inflammatory rheumatic diseases. Taken together, it is hoped that the increasing knowledge in these areas will open up new therapeutic avenues; we will briefly discuss potential future approaches to management of rheumatic diseases using therapies that regulate the complement system.

Competing interests

G. Sturfelt declares an association with Active Biotech. See the article online for full details of the relationship. L. Truedsson declares no competing interests.

The complement system

The many proteins that constitute the complement system can be divided in three different functional groups: proteins involved in complement activation; proteins involved in regulation of complement activation; and cell membrane associated proteins (receptors) that interact with fragments of complement components formed during activation. The complement activation cascade components have a role in at least one of three pathways that all result in generation of C3 convertases, the classical, lectin and alternative pathways, or a shared downstream terminal pathway that leads to the formation of the lipophilic C5b–9-containing membrane-attack complex (MAC) which forms a pore in the target cell and promotes osmotic cell lysis (Figure 1). Components of these activation cascades have other roles in host defense, such as enhancement of phagocytic clearance through opsonization of ICs and foreign or apoptotic cells, direction of leukocyte chemotaxis and regulation of innate and adaptive immune responses. An overview of split products and complexes formed during complement activation and their biological functions is given in Table 1 and Table 2, respectively. Complement receptors (CR) represent an interface between activated complement components and cell membranes (Figure 1) and, as such, mediate many of these processes.

Self surfaces are protected against the destructive activities of complement by the inhibitory action of several proteins at various stages of the activation cascade. For example, C3b and C4b—key components of the C3 convertases that initiate or amplify complement responses—are inhibited by membrane cofactor protein (MCP, also known as CD46) and complement decay-accelerating factor (DAF). CR1 might also contribute to the inhibition of complement activation on a cell surface, although

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the main function of this receptor is in degradation of C3b associated with ICs (Figure 1).¹ Inhibition of complement at the stage of MAC formation is provided by protectin (CD59). In the circulation, control at the level of classical pathway activation through the C1 complex or lectin pathway initiation via complexes of mannose-binding lectin (MBL; also known as mannose-binding protein C) and mannan-binding lectin serine protease (MASP) is accomplished by plasma protease C1 inhibitor (C1Inh). C4b and C3b are inhibited by circulating factor I with C4b-binding protein (C4BP) and factors H and H-like protein 1, respectively, acting as cofactors, whilst building of the C5b–9 complex is regulated by clusterin and vitronectin.

Complement: crossroads and dualism

Several examples of links between the complement system and the adaptive immune systems exist. In humans, complement is a powerful mediator not only of inflammation in defence against invading microbes, but also of inflammation and tissue damage associated with autoimmune and IC-mediated diseases. Complement can induce tissue damage directly through MAC formation or indirectly via deposition of cell-bound split products, such as C4b and C3b, which activate

Key points

- Complement activation is involved in the pathogenesis of many rheumatic diseases
- Deficiencies in components of the classical pathway of complement activation, but not other complement deficiencies, are associated with development of systemic lupus erythematosus (SLE) and SLE-like disorders
- Complement activation via the alternative pathway in tissues can cause damage associated with autoimmune disease pathology
- Increased knowledge of the functions of complement will hopefully lead to identification of new therapeutic targets in rheumatic diseases

CR-expressing leukocytes. Activation of the complement cascades also promotes inflammation by generating anaphylatoxins C3a, C4a and C5a, which are chemotactic and have cell-activating effects via induction of cytokines and other proinflammatory molecules. Furthermore, several studies have shown that complement components stimulate signalling that regulates the phenotype and function of several immune cell subsets;^{2,3} for example, signalling through MCP is involved in T-cell activation.⁴

The complement system is sometimes described as a double-edged sword, owing to its dualistic functions in host defence and in causing injury. The requirement for balance in complement activity is clearly illustrated in SLE. In this disease, complement activation contributes

Figure 1 | Schematic representation of complement activation and important interactions between complement components and cells. The complement cascade can be activated by different stimuli through three main pathways: the classical, lectin and alternative pathways. Each of these pathways leads to cleavage and activation of C3, resulting in the generation of a small phlogistic C3a fragment and a larger C3b fragment that can opsonize pathogen cells and ICs and also bind to the receptor CR1 on host cells. Degradation of C3b by complement factor I in the presence of cofactors (complement factor H, MCP and CR1) creates smaller fragments, iC3b and C3d, that interact with CR3 or CR4 and CR2, respectively, which are present mainly on phagocytic cells and B cells. Further complement activation leads to C5 cleavage and formation of the MAC. The smaller C5 cleavage fragment, C5a, is a potent chemotactic factor for phagocytes and, like C3a, is also an anaphylatoxin causing degranulation of mast cells and basophils through receptor interactions. Abbreviations: B, complement factor B; C3aR, C3a anaphylatoxin chemotactic receptor; C5aR, C5a anaphylatoxin chemotactic receptor; CR, complement receptor; D, complement factor D; H, complement factor H; I, complement factor I; IC, immune complex; MAC, membrane attack complex; MASP, mannan-binding lectin serine protease; MBL, mannose-binding lectin; MCP, membrane cofactor protein; P, properdin.

Table 1 | Complement split products formed during complement activation

Split product	MW (kDa)	Description and/or function
C2a	68	Larger fragment formed by cleavage of C2 during activation Component of the classical pathway C3 convertase C4b2a
C2b	30	Smaller fragment formed by cleavage of C2 during activation
C3a	8	Smaller fragment formed by cleavage of C3 during activation Complement anaphylatoxin Chemotactic to eosinophils Direct antimicrobial effect
C3a-desArg	8	Inactivated derivative of C3a Chemotactic to eosinophils Direct antimicrobial effect
C3b	178	Larger fragment formed by cleavage of C3 during activation Component of the alternative pathway C3 convertase C3bBb Component of the C5 convertases C4b2a3b and C3b _n Bb Opsonin and activation regulator through binding to CR1
iC3b	176	Degradation fragment formed by cleavage of C3b Opsonin through binding to CR3 (CD11b-CD18; integrin $\alpha_M\beta_2$), CR4 (CD11c-CD18; integrin $\alpha_X\beta_2$) and possibly to CR1
C3c	138	Degradation fragment formed by cleavage of C3b
C3d/dg	33–38	Degradation fragment formed by cleavage of C3b containing the C3b covalent binding site Binds to CR2 and regulates B-cell function
C4a	8	Smaller fragment formed by cleavage of C4 during activation Complement anaphylatoxin
C4b	192	Larger fragment formed by cleavage of C2 during activation Component of the classical pathway C3 convertase C4b2a Opsonin and activation regulator through binding to CR1
C5a	11	Smaller fragment formed by cleavage of C5 during activation Complement anaphylatoxin Chemotactic to neutrophils and monocytes Induces apoptosis
C5a-desArg	11	Inactivated derivative of C5a Chemotactic to neutrophils and monocytes
C5b	185	Larger fragment formed by cleavage of C5 during activation Component of the membrane attack complex C5b–C9 _n
Ba	30	Smaller fragment formed by cleavage of factor B
Bb	63	Larger fragment formed by cleavage of factor B Component of the alternative pathway C3 convertase C3bBb and C5 convertase C3b _n Bb Induces apoptosis

Abbreviations: CR, complement receptor; MW, molecular weight.

to inflammation and tissue damage in IC-mediated manifestations, with histopathological findings of complement deposits correlating with clinical symptoms and complement consumption in the circulation. However, seemingly in paradox, complement deficiency states within the classical pathway are associated with a high risk of developing SLE. This dualism is often referred to as ‘the lupus paradox’, and has previously been discussed by Müller-Eberhard⁵ and by Carroll.⁶ We hypothesize that the lupus paradox reflects the complexity of complement-mediated functions; factors derived from C3 and components downstream in the activation sequence cause or promote the cell and tissue damage associated with SLE, whereas initial development of the disease is particularly influenced by deficiencies within the initiating components of the classical pathway, which do not protect from complement-mediated damage. The

evidence that supports this theory is discussed in more detail in the following sections.

Complement deficiency and disease

The occurrence of complete deficiency of a complement protein is a relatively rare finding; nevertheless, deficiency syndromes have been described for most components (Table 3). Complement deficiency states are associated with increased susceptibility to various forms of infections.⁷ Deficiencies of classical pathway complement proteins C1q, C1r or C1s, C2 and C4 are associated with an increased frequency of pyogenic infections,⁷ and also SLE and SLE-like disorders.⁸ A clear hierarchy exists in regards to susceptibility to SLE conferred by various complement-deficiency syndromes, with deficiencies of C1q and of C1r or C1s associated with a high risk (90%) and C4 deficiency a slightly lower risk, whereas individuals with C2 deficiency have an estimated 10–20% risk of developing the disease.⁸ The results of some studies have suggested an association of MBL deficiency with increased susceptibility to SLE,⁹ but no evidence of increased SLE risk was found in an epidemiologically-based investigation.¹⁰ Clear evidence of an increased SLE risk has not been found in individuals with heterozygous C2 deficiency,¹¹ or in individuals with a polymorphic variant of the C1q subunit A encoding gene, which is associated with decreased C1q levels;¹² however, a possible association of this C1q variant with subacute cutaneous lupus erythematosus has been reported.¹²

Genes encoding the complement components that constitute the C3 convertases—C2, C4 and complement factor B—are located in the MHC class III region on chromosome 6. The gene encoding C4 protein is extremely polymorphic, and has been ancestrally duplicated and mutated in the human genome to create two coding gene variants, *C4A* (encoding acidic C4A) and *C4B* (encoding basic C4B). Furthermore, dichotomous long and short forms of both *C4A* and *C4B* genes also exist, owing to the integration of a human endogenous retrovirus, HERV-K(C4).¹³ Moreover, between one and four copies of the genes encoding either C4 isotype—and in the long or short form—can be present on each chromosome; thus, a range of 2–8 copies of C4 genes can theoretically be present, although 0–7 copies have been documented in the diploid genome.¹³ Functional differences between C4A and C4B isotypes have been suggested to influence the risk of developing SLE and severity of the disease. Activated C4A preferentially forms amide bonds with protein antigens, whereas C4B has a propensity to form ester linkages with carbohydrate antigens, such as those found on bacterial cell walls.¹⁴ Homozygous deficiency of C4A has been suggested to be a susceptibility factor for SLE,¹⁵ potentially related to impaired scavenging of ICs in the absence of C4A. No clear disease association to C4 gene copy variation has been shown.

Complement deficiencies affecting the classical pathway—genetically determined or acquired as a result of complement component consumption—are strongly associated with an increased risk of SLE, as stated above,

but not with autoimmune diseases in general. Thus, no indications exist for increased risk of developing other systemic autoimmune diseases, such as rheumatoid arthritis (RA) or systemic vasculitis, in individuals with complement deficiency. The reason for the association between complement deficiencies, particularly in the classical pathway, and risk of developing SLE or SLE-like disorders is not clear, but four hypotheses can be identified (Figure 2); the data that support these theories are discussed in the following sections.

Impaired handling of ICs

A well-documented finding is that complement deficiency reduces the capacity to solubilise ICs.^{16,17} Complement solubilisation of ICs mediates their transport from tissues to the reticuloendothelial system via interaction with blood cells expressing complement receptors.¹⁶ Kinetic studies have demonstrated the importance of the classical pathway for effective opsonization of ICs,¹⁷ which enables efficient recognition of such materials and their removal from the circulation.

Aberrant induction of tolerance

Defective induction of immune tolerance is another hypothesis—based mainly on data from animal models—that might explain the association of complement deficiencies with SLE or SLE-like disorders.¹⁸ Self antigens are coated with complement fragments and delivered to the specific B cells by binding to complement receptors thereby enhancing the elimination of the self-reactive cells. Complement deficiency could thus lead to inefficient elimination of self-reactive B cells, which, in the presence of T-helper cells, could be activated to produce autoantibodies. Presumably, autoreactive T cells could also contribute to defective immune tolerance and increased autoantibody production.

Deficient scavenging of apoptotic cells

In the late 1990s, the complement system was found to be involved in scavenging of apoptotic cells; in 1997, Korb and Ahearn¹⁹ demonstrated that C1q can bind directly to apoptotic cellular material in absence of antibodies. Data from a study in C1q knockout mice published the following year²⁰ suggested that the role of complement in clearance of apoptotic material explained the relationship between deficiencies in classical pathway components and the risk of developing SLE. Delayed clearance of apoptotic cells can lead to secondary necrosis, which could increase tissue inflammation and activation of self-reactive B cells and T cells. We have shown in an *in vitro* model that C1q was not more important for clearance of apoptotic cells than other components of the classical pathway and that components of the alternative and lectin activation pathways had less influence on the phagocytosis of such material.²¹

Deficient control of cytokine production

Studies have indicated that complement components are important regulators of cytokine production.²² For example, our group found that C1q is able to inhibit or

Table 2 | Complexes formed during complement activation

Complex	Description and/or function
C1INH–C1r–C1s	Intermediate complex formed during activation of C1
C1INH ₂ –C1r–C1s	Complex formed during activation of C1
C4b2a	C3 convertase of the classical pathway
C4b2a3b	C5 convertase of the classical pathway
C3bBb	C3 convertase of the alternative pathway
C3b _n Bb	C5 convertase of the alternative pathway
C5b–8	Incomplete membrane attack complex
C5b–9 _n	Membrane attack complex, which induces cell proliferation and apoptosis
C5b–9–S	Membrane attack complex with protein S (membrane attack inhibited) Soluble terminal complement complex

augment the *in vitro* production of IFN- α —a key cytokine in the pathogenesis of SLE—by peripheral blood mononuclear cells or plasmacytoid dendritic cells (pDCs), depending on the stimulus used;²³ notably, IFN- α secretion in response to CpG DNA and ICs in pDCs was inhibited by C1q, whereas C2 and C4 did not have this effect.²³ Together, the findings discussed provide potential explanations for the hierarchy that exists among deficiency states within the classical pathway in regards to the development of SLE.

Complement activation in disease

Activation of the complement system results in the production of a series of phlogistic proteins with potent biological effects. This process is usually an important defence mechanism, but can turn into a pathogenetic mechanism if not properly regulated and/or when autoantibody formation is intense, owing to formation of ICs in tissues or entrapment of circulating ICs. Aberrant complement activation has been demonstrated to be of importance in several rheumatic diseases such as SLE, RA and systemic vasculitis.

Systemic rheumatic disorders

The idea that complement activation is involved in the pathogenesis of SLE originates from observations of consumption of complement components, especially those of the classical pathway, in this disease (Figure 2). Complement consumption can manifest as decreased levels of the proteins in the circulation and also increased complement and immunoglobulin deposits in affected organs, such as the kidneys and skin; investigations of these organs form the basis of most studies on SLE pathogenesis. SLE is characterized by breakdown of tolerance against nuclear self antigens, which probably originate from the nuclei of dying cells, and associated proteins. ICs containing such antigens are deposited in different parts of the body and promote inflammation and tissue damage. Furthermore, chronic activation of pDCs by ICs and subsequent production of type I interferons (IFNs) seems to be central to the pathogenesis of SLE.²⁴ Strong support for pathogenetic effects of complement in SLE comes from correlations between clinical findings and the

Table 3 | Summary of complement deficiencies in humans

Complement component involved	Frequency	Main disease association(s)	Reference(s)
C1q	50–100 reported cases	SLE; glomerulonephritis; infections	Skattum <i>et al.</i> ⁷
C1r or C1s	10–50 reported cases	SLE; glomerulonephritis	Wu <i>et al.</i> ¹⁰⁶
C2	Estimated prevalence 1/20,000*	SLE; infections	Skattum <i>et al.</i> ⁷
C3	20–50 reported cases	SLE; glomerulonephritis; recurrent infections	
C4	20–50 reported cases	SLE; glomerulonephritis; infections	
MBL	Estimated prevalence 1/10*	Susceptibility to infections	
Factor D	<20 reported cases	Neisserial infections	
Properdin	50–100 reported cases	Meningococcal disease	Fijen <i>et al.</i> ¹⁰⁷
C5, C6, C7 or C8	20–100 reported cases	Usually healthy; recurrent neisserial infections	Skattum <i>et al.</i> ⁷
C9	<10 reported cases Estimated prevalence 1/1,000*	Usually healthy	Skattum <i>et al.</i> ⁷ Witzel-Schlömp <i>et al.</i> ¹⁰⁸
C1Inh	Estimated prevalence 1/50,000 [§]	Hereditary angioedema	Skattum <i>et al.</i> ⁷

*Estimated prevalence in white populations. †Rare deficiency in white populations, but common in the Japanese population (prevalence of about 0.1%).
[§]Heterozygous deficiency. Abbreviations: C1Inh, plasma protease C1 inhibitor; MBL, mannose-binding lectin; SLE, systemic lupus erythematosus.

presence of immune deposits in affected tissues, associations between circulating, deposited and eluted ICs, and from a large number of animal studies.²⁵

Complement activation in lupus nephritis

Immunoglobulins against double-stranded DNA (anti-dsDNA antibodies) are generally accepted to be involved in the pathogenesis of lupus nephritis in most cases;²⁶ for example, anti-dsDNA antibodies have been eluted from affected kidneys in experiments involving animal models of lupus.²⁷ However, uncertainty remains regarding the extent of IC deposition from circulation compared with local formation resulting from cross-reactions between anti-dsDNA antibodies and α -actinin, laminin or other glomerular constituents.²⁸ Anti-dsDNA antibodies binding to nucleosomes that are trapped in glomeruli by aberrantly expressed laminins or other glomerular constituents has been proposed as a mechanism of IC formation in lupus nephritis.²⁹ That initial lesions in kidneys involved in SLE are seen in glomeruli is well established, with the most pronounced immune deposits being observed in proliferative glomerulonephritis (diffuse global glomerulonephritis; WHO grade IV or the International Society of Nephrology–Renal Pathology Society's [ISN–RPS] IV-G classification).³⁰ In lupus nephritis in particular, these morphological characteristics are associated with decreased plasma levels of C1q, C2, C4 and often C3 (especially in severe nephritis),³¹ suggesting the pathogenetic mechanism involves IC-mediated activation via the classical pathway. In focal or segmental glomerulonephritis (WHO grade III or ISN–RPS classification IV-S), IC-containing deposits may be scarce or even absent;³² thus, the pathogenesis has been suggested to be different from that of diffuse global nephritis and possibly more analogous to the pauci-immune nephritis seen in patients with systemic vasculitis.

Complement proteins as autoantigens

Evidence suggests that complement components might also be targets of autoantibody responses, which are usually directed against modified proteins and not native

components. Anti-C1q antibodies are seen in approximately 30–40% of patients with SLE and especially in patients with proliferative nephritis.³³ C1q-specific IgGs recognise the collagenous portions of C1q molecules that present as a neoepitope on protein binding, and which are not exposed on fluid-phase C1q.³⁴ Indeed, evidence suggests that anti-C1q antibodies can be involved in the pathogenesis of lupus nephritis by binding to solid-phase C1q present locally in the kidney, including C1q bound to early apoptotic cells.^{35,36} In addition, antibodies against C1s and C1Inh have been reported in patients with SLE, but the potential pathogenetic effects of these autoantibodies have not been defined. C3 and C4 nephritic factors are IgG autoantibodies with the capacity to stabilize C3 convertases of the classical and alternative pathways, and could therefore be involved in the pathogenesis of nephritis.³⁷ Autoantibodies against complement regulators and receptors have been reported, and functional deficiency caused by antibodies against complement factor H has been suggested to be of clinical importance in nephritis based on data from animal models.³⁸

Complement and microparticles in SLE

Increased complement activation through the classical pathway in SLE has also been reported to be reflected in the composition of cell-derived microparticles.³⁹ Increased loads of IgG, IgM and C1q were seen on microparticles derived from patients with SLE compared with those from patients with RA or systemic sclerosis, or from healthy individuals.³⁹ The microparticles could be a source of immunogenic autoantigens that are accessible for autoantibody binding, and IC formation on these particles might contribute to complement activation in SLE.

Complement and neutrophil activation

Observations made in a number of studies give support to a possible role for neutrophil extracellular traps (NETs)—structures with bactericidal activity comprising chromatin fibres and other cellular components—in the pathogenesis of SLE and especially lupus nephritis. Complement activation with subsequent C5a

anaphylatoxin chemotactic receptor (C5aR) involvement primes viable neutrophils to undergo NETosis—a specialised form of cell death—where the neutrophils expel NETs into the extracellular environment.⁴⁰ NETs are a potential source of autoantigens such as DNA, and impaired degradation of these structures, which is partially dependent on anti-NET antibodies, seems to be strongly associated with kidney involvement in SLE.⁴¹ In addition, CR3 (CD11b–CD18; integrin $\alpha_M\beta_2$), which mediates neutrophil activation, has been suggested to be of importance.⁴² Furthermore, NETs might activate pDCs in SLE, by presenting self-DNA–peptide complexes that interact with Toll-like receptor 9 in these cells.⁴³ Thus, a role for complement in regulation of NET formation or breakdown could be of pathogenetic importance in SLE and SLE-like disorders.

Complement split products have been reported to activate neutrophils and platelets (through mechanisms similar to those that promote NETosis in the former), resulting in occlusive vasculopathy owing to their aggregation and adherence to vascular endothelial cells.^{44–46} Moreover, evidence suggests that stimulation with C5a, as well as MAC formation, might cause cells to release microparticles with procoagulant activities.⁴⁶ More recently, C4d deposits have been reported on red blood cells after incubation with sera from patients with SLE, but not with control sera.⁴⁷ These deposits were associated with biochemical changes in the erythrocyte and decreased cell membrane deformability,⁴⁷ which could conceivably affect the microcirculation and impair delivery of oxygen to tissues. The complement-mediated effects on the vasculature described above could contribute to SLE manifestations including central nervous system ischemia, pulmonary vasculitis and pancreatitis.

C-reactive protein and complement activation

The classical pathway can be activated not only by target-bound antibodies or ICs but also by breakdown products of apoptotic cells, C-reactive protein (CRP) and lipopolysaccharides.⁴⁸ These mechanisms of complement activation could be of pathogenetic importance in SLE and might contribute to tissue damage. However, high serum levels of soluble CRP have been shown to inhibit complement activation.⁴⁹ The clinical relevance of this finding is unclear, as disparate results have been obtained with CRP supplementation in mouse lupus models.^{50,51}

Complement in antiphospholipid syndrome

Antiphospholipid syndrome (APS) is closely related to SLE, and is a condition in which pathogenic, complement-activating antibodies target various phospholipids and phospholipid-binding proteins that have an essential role in homeostasis of the coagulation system.⁵² The importance of complement activation to the pathogenesis of APS has been shown in relevant animal models;^{52,53} for example, reduced thrombus generation and foetal loss has been demonstrated in a mouse model of APS after inhibition of C3 convertase using a soluble CR1-related protein γ (Crry)–immunoglobulin chimera.⁵³ Furthermore, patients with SLE associated

Figure 2 | Complement in the pathogenesis of SLE. Evidence suggests that autoantigens derived from apoptotic cells, and possibly also neutrophil extracellular traps and microparticles, are involved in the generation of autoantibodies that underlie the pathogenesis of SLE. In a genetically predisposed individual, these processes are thought to give rise to a sustained immune reaction resulting in the disease. Deficiency or aberrations in components of the classical pathway of complement activation, either genetically determined or caused by excessive activation and consumption, might be part of the pathogenetic process on multiple levels: impaired scavenging of autoantigens; compromised immune tolerance to self antigens; defective autoantibodies and IC removal; and dysregulated cytokine production. Increased complement activation, as well as causing complement consumption and deficiency, can participate in tissue damage such as glomerulonephritis, which is a hallmark of SLE. Such damage provokes further inflammation and additional complement aberrations, which could contribute to a vicious circle of reactions preventing termination of the disease process. Abbreviations: IC, immune complex; IFN, interferon; SLE, systemic lupus erythematosus; UV, ultraviolet.

with C2 deficiency seem to be protected from thrombotic events, despite the presence of antiphospholipid antibodies in a large proportion of these individuals.⁵⁴

Complement-mediated tubulointerstitial damage

Vascular and tubulointerstitial damage are of utmost importance for prognosis in SLE-associated kidney disease. The involvement of complement activation in tubulointerstitial inflammation and damage, including demonstration of a pathogenetic effect of C5aR signalling, has been demonstrated in animal models.⁵⁵ In MRL^{lpr} mice, complement factor H deficiency clearly accelerates the development of lupus nephritis, in terms of both glomerular and tubulointerstitial inflammation.⁵⁶ Interestingly, although no mutations in genes encoding complement regulatory proteins have yet been shown to predispose individuals to SLE or nephritis, MCP and complement factor H polymorphisms have been associated with age at onset of lupus nephritis.⁵⁷

Complement involvement in skin manifestations

Complement is involved in various skin manifestations of SLE, and is usually found deposited in the dermo-epidermal junction together with immunoglobulins of all major classes (IgG, IgM and IgA).⁵⁸ DNA released from keratinocytes after ultraviolet-light-induced injury might

Figure 3 | Complement in the pathogenesis of rheumatoid arthritis. In the synovial compartment ICs are formed, comprising various autoantibodies and autoantigens. These complexes activate complement leading to generation of proinflammatory complement fragments and complexes, which interact with cells causing release of cytokines and proteases. Activation of C5 seems to be most important in driving the damaging inflammation. Some proteases might be able to cleave C3 and thereby increase complement activation (extrinsic pathway). Several extracellular matrix proteins interact with complement and could modulate these processes. Fibromodulin and osteomodulin (also known as osteoadherin) bind C1q and can initiate classical pathway activation, but bind also C4BP and complement factor H, which inhibit complement activation. Decorin and biglycan might also modulate complement activation by binding C1q without initiating activation. Abbreviations: C4BP, C4b-binding protein; H, complement factor H; IC, immune complex; MAC, membrane attack complex.

bind type IV collagen and serve as antigen for antinuclear antibodies.^{59,60} In patients with SLE, linear immunoglobulin and complement containing deposits similar to those found in skin lesions are often also found in uninvolved skin, a feature that can be useful for diagnosis.

Complement in Sjögren's syndrome pathogenesis

Sjögren's syndrome (SS) is an autoimmune disorder closely related to, and often coexisting with, SLE and other inflammatory connective tissue disorders. As in SLE, null alleles for C4A are common.⁶¹ The presence of these null alleles is a common reason for observation of slightly lower than normal C4 serum levels in patients with SS and/or SLE.⁶¹ Both in patients with SLE⁶² and individuals with SS,⁶³ slightly low levels of C4BP are often recorded during periods of active disease.

Complement in myositis and systemic sclerosis

A proposed initial event in the pathogenesis of dermatomyositis and polymyositis is the activation of complement in response to antibodies directed against endothelial cells and subsequent MAC formation;⁶⁴ deposits of C3b, C4b and MAC are found on capillaries and could be related to muscular ischemia and capillary loss.⁶⁴ Hypocomplementaemia—possibly resulting from increased complement-component consumption—in dermatomyositis, polymyositis and systemic sclerosis is preferentially seen in patients with manifestations that overlap with other diseases, especially SLE. Nevertheless, evidence suggests that complement activation related to dysfunction of regulatory proteins could contribute

to the inflammatory process and vascular damage in these diseases.⁶⁵

Rheumatoid arthritis and other arthritides

Evidence of a role for complement in RA

The evidence for complement activation as a mediator of joint and extra-articular inflammation in RA is strong. Interestingly, the results of a 2011 study suggest that increased serum levels of C1q, caused by genetic variation, could increase the risk of developing RA, possibly owing to increased capacity for activation via the classical pathway.⁶⁶ Moreover, a role for local intra-articular activation of complement in RA is supported by observation of decreased total haemolytic complement activity and reduced levels of individual components in synovial fluid.^{67,68} Studies of complement component cleavage products supported this interpretation.⁶⁹ On the other hand, patients with spondyloarthritis, who have less-erosive arthritic manifestations, usually do not show evidence of overt complement activation.⁷⁰

Findings in mouse models of inflammatory arthritis have revealed that complement is critically involved in inflammatory joint damage.⁷¹ C5a has been implicated as an important mediator of joint injury; therefore, C5a-neutralizing antibodies would be expected to counteract development of disease. Indeed, a vaccine inducing anti-C5a antibodies—which do not markedly compromise C5 or C5b activity—has been proven effective in the prevention of antibody-mediated C5a-dependent inflammatory disease in mouse models.⁷²

Mechanism of complement-mediated damage in RA

An overview of the pathogenetic complement-dependent process that might be involved in RA is provided in Figure 3. In patients with RA, a wide range of autoantibodies can be present, many of which are able to bind to joint antigens and form ICs in the inflamed synovial tissue (pannus) and cartilage, resulting in complement activation and consumption of complement components. As a consequence, activation products such as C1Inh–C1r–C1s complexes, C2a, C3a, C3d or C3dg and C5a are found at increased levels in synovial fluid.^{70,71} Furthermore, complement deposition can be demonstrated in the synovial tissue by immunohistological staining.⁷³ These complement proteins attract and activate macrophages, mast cells, fibroblasts and neutrophils, with subsequent release of proteolytic enzymes leading to tissue damage. The MAC can probably potentiate the inflammatory process by stimulation of collagenase production and release by fibroblasts (Figure 3), as indicated by the results of *in vitro* studies.⁷⁴ Indeed, findings from a mouse model have implicated effector mechanisms initiated by C3aR, C5aR and MAC in the pathogenesis of RA.⁷⁵

Complement activation pathways in RA

Synovial fluid from patients with RA contain micro-particles originating from apoptotic granulocytes,⁷⁶ which can potentially activate the classical pathway in a similar way to circulating ICs. Thus, C1q, C3 and C4 deposits

are found on microparticles,⁷⁶ and correlations are found between circulating ICs and classical pathway activation products in synovial fluid,^{76,77} suggesting a role for microparticles and complement activation in joint pathology. High levels of Bb fragments have also been found in synovial fluids from patients with RA,⁷⁸ providing evidence that activation of the alternative pathway might be involved in the pathogenesis of this disease.

Citrullinated proteins produced by post-translational protein modification, in which arginine residues are converted to citrulline, seem to be immunogenic and thereby arthritogenic. Citrullinated proteins and antibodies against these proteins are frequently observed in synovial tissue from patients with RA.⁷⁹ Consistent with these findings are observations that anti-cyclic citrullinated peptide (anti-CCP) antibodies activate both the classical and alternative pathways of the complement system.⁸⁰ In addition, type II collagen⁸¹ and IgA-containing ICs⁸² might be activators of the alternative pathway in RA. Of importance is the realization that the alternative pathway acts as an amplification loop of classical pathway activation (Figure 1), and thus these mechanisms could potentially exacerbate complement-mediated injury in RA. As is the case for SLE,⁹ limited evidence exists to suggest that the lectin pathway is of importance in the pathogenesis of RA; however, MBL deficiency seems to contribute to RA severity, showing an association with increased risk of erosive disease.⁸³

A number of cartilage molecules have been identified that bind complement proteins. Examples are decorin and biglycan, which bind but do not activate C1q (Figure 3). By contrast, fibromodulin and osteomodulin (also known as osteoadherin) bind to collagen fibres in cartilage and interact with the globular heads of C1q, leading to activation of the classical pathway;^{84,85} however, these proteins also bind C4BP and complement factor H, which limits complement activation to the early part of the classical pathway (Figure 3).^{84,85} Nevertheless, low-level complement activation might contribute to chronic inflammation in the damaged joint. On the other hand, findings suggest that decorin, biglycan and possibly cartilage oligomeric matrix protein (COMP) inhibit C1 activation, which could be protective.^{86,87} COMP also binds MBL, inhibiting the lectin pathway, but might activate the alternative pathway by interacting with properdin and C3, which could be of importance for development of cartilage and bone damage in RA.⁸⁷ Indeed, COMP–C3b complexes have been detected in sera from patients with RA, and have been implicated as markers of this disease.⁸⁷

Extra-articular disease and other arthritides

RA is a heterogeneous disease and is associated with extra-articular manifestations, which have an important influence on the outcome of the disease. In rheumatoid systemic vasculitis in particular, complement activation by ICs deposited in the affected tissues is of pathogenetic importance.⁸⁸ Furthermore, hypocomplementaemia, with decreased C3 and C4 plasma levels suggestive of increased complement activation, is commonly observed

in patients with severe extra-articular manifestations, such as mononeuritis multiplex.⁸⁹

Studies of complement activity in other arthritides, such as psoriatic arthritis, ankylosing spondylitis and reactive arthritis, are relatively scarce. Evidence of complement activation in osteoarthritis (OA) and spondyloarthritis—increased amounts of C1Inh–C1r–C1s complexes and C3d fragments and decreased levels of C3 and C4—was not found in synovial fluid in a study by Sjöholm and co-workers,⁷⁰ despite clear evidence of inflammation. Another report supported these observations,⁷³ and demonstrated marginal involvement of complement in reactive arthritis, with local deposition of C3b and C9 in synovial tissue.⁷³ By contrast, a 2011 study demonstrated the importance of complement activation in the pathogenesis of OA, as components of the classical pathway, alternative pathway, and the MAC were found to be aberrantly expressed in patients with this disease;⁹⁰ the authors suggested that extracellular matrix proteins, such as fibromodulin, could contribute to this process.⁹⁰ Increased formation of MAC resulted in stimulation of chondrocytes to produce proinflammatory factors and matrix-degrading enzymes *in vitro*, and C5 deficiency protected against surgically-induced OA in a mouse model.⁹⁰ On the basis of these findings, individuals with reduced functional activity of complement regulatory proteins could potentially have an increased risk of developing OA, as a result of increased C3 and C5 activation.

Systemic vasculitis

A number of studies have shown that complement is involved in the pathogenesis of systemic vasculitis. Strong evidence demonstrating the importance of the alternative pathway in the pauci-immune process of antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis has been obtained from relevant animal models. Mice lacking C5, complement factor B,⁹¹ or C5aR⁹² are protected from anti-myeloperoxidase IgG-induced glomerulonephritis, and inhibition of C5 activation using an anti-C5 antibody ameliorated disease in this model.⁹³ Furthermore, C3a and C5a were generated from normal serum by supernatants produced by TNF-primed neutrophils stimulated with IgG from patients with ANCA-associated disease, but not with IgG from healthy individuals;^{91,92} the conditioned supernatants were also able to sensitize neutrophils for ANCA-mediated activation via the C5aR.⁹² The studies demonstrated that neutrophils primed with low doses of cytokines and coagulation factors show evidence of alternative pathway activation followed by enhanced neutrophil activation and recruitment. On the basis of these findings, complement activation via the alternative pathway has been suggested to be an important positive feedback amplification mechanism in neutrophil-mediated diseases.^{91,92}

In patients with Behçet disease, perivascular deposits of complement components C3 and C4 are found at high frequency in cutaneous and mucocutaneous lesions.⁹⁴ Furthermore, the deposits are observed in the dermo-epidermal junctions within, or in proximity to, skin lesions at a similar frequency as in patients with SLE.⁹⁴ Thus, some

evidence indicates that complement might be involved in the pathogenesis of Behçet disease, but more studies and support from animal models of this disease are required.

Hypocomplementaemic urticarial vasculitis syndrome (HUVS) is a disorder clinically characterized by erythema, hives, hypocomplementaemia and production of anti-C1q autoantibodies. The disease can be difficult to differentiate from SLE, but anti-C1q autoantibodies obtained from patients with HUVS are usually directed against B-chain and C-chain epitopes of the C1q molecule, whereas in SLE anti-C1q autoantibodies usually target the conformational epitopes in the assembled molecule.⁹⁵ The difference in specificity of these autoantibodies could have implications for complement activation and the pathogenesis of these diseases. ICs containing anti-C1q autoantibodies are found in the circulation of patients with HUVS and activate the classical pathway in blood vessel walls, leading to mast cell degranulation and increased vascular permeability and leukocytoclastic vasculitis.⁹⁶ Anti-C1q autoantibodies can crossreact with lung surfactant factor proteins in both HUVS and SLE, resulting in lung disease.⁹⁶

Complement-directed therapies

On the basis of data demonstrating an important pathogenic role of complement in rheumatic diseases and the effects of complement inhibition in animal models, this system has been suggested to be an interesting target for therapy. Two main goals of such therapies are reconstitution in complement-deficiency states and inhibition of complement activation in diseases in which strong evidence suggests that activation causes damage. Other possible aims of complement-targeted therapeutics are strengthening of the defence against certain infections and improvement of antibody responses to vaccines. A detailed discussion of development of complement-directed therapeutics is beyond the scope of this Review and has been reviewed elsewhere.⁹⁷

Complement component supplementation

Prevention of disease through supplementation of missing complement components has been attempted in various deficiency syndromes.⁷ The most successful results have been obtained with C1Inh concentrate, which is now licensed in many countries and routinely used to correct deficiency of this protein.⁹⁸ Plasma-derived MBL has been tested in patients deficient for MBL,⁹⁹ and this product—as well as recombinant MBL preparations—might be beneficial in carefully selected cases. Patients with C1q or C2 deficiency have been treated with regular infusions of plasma and clinical improvements have been reported.^{100,101} In C1q deficiency, another possible method of complement protein supplementation is stem cell transplantation, as C1q is produced by bone marrow derived cells.

Complement inhibiting agents

Treatments comprising antibodies that target complement components have been shown to reduce tissue damage after myocardial infarction and stroke,¹⁰² which are

important late organ manifestations in rheumatic diseases. The results of studies using animal models suggest that antibodies that block C5 and C5aR activity are promising biologic treatment options in systemic vasculitis¹⁰³ and other rheumatic conditions.¹⁰⁴

Vaccination has been a successful approach to the prevention of infections in individuals with complement deficiencies, which occur in patients with SLE (Table 3), as discussed above.⁷ Conversely, animal studies suggest that vaccination against complement components could be a future option in prevention of inflammatory rheumatic disorders that are dependent on aberrant complement activation, particularly involving C5a and C5aR.⁷² Adjuvant effects of C3d fragments on binding to CR2 receptors on B cells have been used in vaccine development.¹⁰⁵

In the near future, complement-directed therapy will probably become an alternative in both acute and chronic clinical disorders, including a number of rheumatic diseases. However, long-term complement inhibition could be complicated by increased risk of infections and potentially autoimmunity. Future developments that enable balanced regulation of complement activation will open avenues towards safe therapeutic control of complement in rheumatic and other diseases.

Conclusions

Complement activation is of importance in the pathogenesis of several inflammatory and also degenerative rheumatic disorders. Furthermore, deficiency states within the classical pathway are closely associated with, and might predispose to, development of SLE and SLE-like disorders, but not to autoimmunity in general. Other complement deficiencies do not increase risk of autoimmune disease, but almost all increase susceptibility to bacterial infections. Local activation of complement in tissues affected by rheumatic diseases, especially via the alternative pathway, is often not reflected in signs of complement activation in body fluids such as blood, and can cause tissue damage that contributes to disease pathology. The increased understanding of complement function in rheumatic and other inflammatory diseases has identified pathways and components of this system as potential therapeutic targets, and initiated the development of potential new treatments.

Review criteria

A large number of potential references were collected for this Review by searching PubMed, MEDLINE and the Lund University library database LibHub as well as the personal collections of the authors. We performed a systematic review of articles published up to January 2012 using MeSH terms “complement” together with “systemic lupus erythematosus”, “rheumatoid arthritis”, “extraarticular manifestations of rheumatoid arthritis”, “spondylarthropathy”, “psoriatic arthritis”, “osteoarthritis”, “systemic sclerosis”, “polymyositis”, “dermatomyositis”, “Sjögren’s syndrome”, “systemic vasculitis”, “Wegener’s granulomatosis”, “microscopic polyangiitis” and “Behçet’s disease”. The references were limited to papers published in the English language and were selected according to relevance to the topic.

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Author contributions

G. Sturfelt and L. Truedsson contributed equally to researching data for the article, discussions of the content, writing the article and review and/or editing of the manuscript before submission.